after an individual has received a primary series of three injections and approximately five booster innoculations of plague vaccine, a plateau in passive hemaggulutination titer is achieved, which is not exceeded by further immunizations and that long-term interruptions of booster injection [illegible] did not result in a marked decline in these antibody titers. They have also demonstrated that 86 percent of 29 vaccines developed a demonstrable passive hemmagglutination titer (geometric mean titer of 1:27) within 60 days after one injection of 1 mL of plague vaccine; and that 90 percent developed significant titers (geometric mean titer of 1:140) within 15 days after receiving a second dose of 0.2 mL 1½ months after the first dose. A booster dose of 0.2 mL given 6 months after the second dose resulted in a geometric mean titer of 1:576 15 days later in 93 percent of the vaccines. As is the case with all vaccines, it would be of great advantage to have serological tests or reproducible animal systems that correlate closely with protective value for man. For plague, a standardized mouse protection test (reported as mouse protection index) has been considered to be valuable. Mouse protection indices of 10 or less have been associated with immunity against plague. The average mouse protection index for sera collected from nonimmune subjects is 16; mouse protection index values of ≦5 are observed in sera collected from patients convalescing from plague. There is a reasonable correlation between a passive hemagglutination titer of ≧1:128 and mouse protection index of ≦10; however, in one series the correlation failed to hold in 6 to 36 subjects (17 percent).

Special Problems

1. The available data concerning immune responses in man have not been incorporated into recommendations for use of the product.

2. The following recommendations on plague immunization should be considered:

a. A primary series of three intramuscular injections (1 mL, 0.2 mL, and 0.2 mL) 1 and 6 months apart, respectively.

b. Booster intramuscular inoculations of 0.2 mL at 12, 18, and 24 months.

c. Where technically feasible, serological testing for passive hemagglutinating antibodies should be done 1 month after each of the booster inoculations (mouse protection index tests would also be useful but are less generally available).

d. In persons achieving a titer of 1:128 after the third and fifth inoculation, further booster does should be administered under the following circumstances:

(1) When the passive hemagglutination titer falls below 1:32.

(2) Empirically every 2 years when the patient cannot be tested serologically.

3. The percentage of individuals who are apparently nonresponders is of concern. However, such individuals may well have partial protection against *Yersinia pestis* in spite of a total failure to demonstrate immune responses by laboratory tests. Again drawing from the experience in Vietnam, there was no obvious problem posed by the projected 8 percent of persons who fell into this category of nonresponders. In fact, some special forces personnel, demonstrated to have been seronegative prior to their service in areas with considerable plague activity, were observed to seroconvert without specific plague-like illnesses during their field service. Again the possible role of antibiotic usage could not be evaluated as a modifier in this situation.

4. It is obvious that regular serological testing can be followed only among selected small groups such as laboratory workers, field personnel, epidemiologists, etc., and cannot be applied to the massive inoculation programs such as used by the military or in other population groups where the risk is deemed sufficient to necessitate immunization. Where serological monitoring is not feasible, booster doses should be administered empirically every 2 years after the fourth or fifth booster dose has been given (about 2 years after the primary series was begun).

Recommendations

1. *Animal models.* In view of the difficulties with field trials, there continues to be the need for the development of animal systems that can be closely correlated with serological responsiveness on the one hand and protective efficacy in man on the other. Such an animal model or test system is not currently available.

2. The available data regarding immune responses should be reflected in recommendations for use of the product.

3. Plague vaccine U.S.P. (E medium) is judged by the Panel to be safe and effective. Revised labeling for civilian use of plague vaccine, following an amendment of license in November 1974, has not been seen by the Panel and remains to be reviewed.

Basis for Recommendations

Judgment of efficiacy in the case of plague vaccine is based upon epidomiological evidence obtained in military populations rather than formal field trials or serological data directly correlated with protection in man. Nonetheless, the Panel believes that the plague vaccine as prepared for military use should be classified in Category I because the available data provide evidence of efficacy. The Panel believes that the data obtained from this epidemiologic investigation and adequate to substantiate effectiveness in this case.

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SPECIFIC PRODUCT REVIEW

Plague Vaccine Manufactured by Cutter Laboratories, Inc.

1. *Description.* This is a suspension of whole plague bacilli (*Yersinia pestis,* strain 195/P) formalin killed in a concentration of 2 thousand million organisms per mL. The suspending medium contains 0.9 percent sodium chloride U.S.P., 0.04 percent formalin, 0.5 percent phenol as a preservative, and only trace amounts of beef heart extract, yeast extract, agar, and hydrolysed derviatives of soya casein and agar. A difference between the composition of the military and civilian products has been resolved.

2. *Labeling*—a. *Recommended use/indications.* The vaccine is recommended for use in persons who have to be present in known plague endemic areas. The scheduled dose for adutls is 1.0 mL, intramuscularly followed 3 months later bv a dose of 0.2

mL intramusculary. Proportionately smaller doses are specified for children aged 6 to 9 and for children aged 6 months to 5 years. Booster doses are recommended at 6 monthly intervals during residence in known plague endemic areas and consist of 0.2 mL intramuscularly. The standard precautions concerning the use of individual presterilized needles and syringes are included.

b. *Contraindications.* The labeling states that there are no real contraindications but advises not to give injections during upper respiratory infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This vaccine meets Federal requirements. Massive information is given concerning the immune response in rabbits and monkeys and the protection achieved in guinea pigs and mice.

Extensive data are available to show that the vaccine produces and antibody response in most recipients. Evidence that the vaccine was effective in protecting U.S. military personnel in Vietnam is provided in the work of Cavanaugh (Refs. 1 and 2).

b. *Safety*—(1) *Animal.* This vaccine meets Federal requirements.

(2) *Human.* Extensive clinical trials in man are cited in the submission to the Panel (Ref. 3) showing the occurrence of sore, swollen, and red arms in a small percentage of subjects receiving their first injections, and in a far greater percentage receiving a full dose as a second injection (this is the reason that the recommended second dose is now 0.2 mL). An isolated reference is cited (Ref. 4) calling attention to the observation in 1 military clinic of 22 patients manifesting urticaria or other Type I allergic reactions after an injection of plague vaccine. The author describes skin tests on these subjects that support the belief that the reactions were due to the vaccine and not to constituents of the medium. The author makes no attempt even to estimate the relative frequency of such reactions.

A great deal of additional data concerning reactions to this vaccine are available in the literature.

c. *Benefit/risk ratio.* In view of the data available that support the belief that the plague vaccine under consideration provides a significant degree of protection against plague, it is considered that the use of this vaccine in individuals who are liable to be exposed to plague is entirely justified. Therefore the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* The vial and package labels are clearly and explicitly marked. The package insert is on the whole much better then average. It is quite clearly written; however, Cutter Laboratories should provide a revised package insert based on civilian use.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Typhoid Vaccine

Typhoid fever is a worldwide disease caused by the bacillus *Salmonella typhi,* which probably affects well over 1 million people a year. It consists of an infection starting in the lower small intestine but spreading to produce septicemia which, if not adequately treated, can cause many weeks of illness; the death rate, prior to antibiotic therapy, was 10 to 15 percent. Recently, strains that are resistant to antibiotics have appeared in several parts of the world, so that the risk of contracting a severe, prolonged illness if infected with *Salmonella typhi* is still present. Infection results from the consumption of food or water that has been contaminated directly or indirectly by the excretions of a case or a carrier. The disease is uncommon in the United States but quite common in almost all countries with unsatisfactory sanitation.

Typhoid vaccine is therefore widely used to protect travelers and others who may run a significant risk of contacting the infection.

Nature of Product

Typhoid vaccine consists of whole typhoid bacilli (*Salmonella typhi*), killed and preserved in any one of several ways. It is usually distributed as a suspension in saline or buffered saline at a concentration of 1 billion organisms per mL. One manufacturer supplies it—on military contract—as an acetone-killed and dried powder, together with a vial containing a suitable reconstituting fluid. The strain of *Salmonella typhi* used by all manufacturers is strain Ty 2.

The use of combined typhoid, paratyphoid A and B vaccine ("TAB" or "Triple typhoid vaccine"), was discontinued in the United States because there is no evidence for the efficacy of the paratyphoid A component, and the paratyphoid B component was found to be effective only in much larger concentrations than were included in "TAB" vaccines.

Production

The typhoid bacillus is usually grown for 24 hours at 35 to 37 °C on veal infusion agar, and washed off with saline as a concentrated suspension. It is killed by heat, phenol, thimerosal, or acetone, and resuspended at the indicated concentration, with either 0.5 percent phenol or 0.01 percent thimerosal added as a preservative. (The product for military use is prepared as noted earlier.) One manufacturer grows it in a semisynthetic medium in a fermenter. Some manufacturers centrifuge and crude harvest, discard the supernatant, and resuspend the sedimented bacteria in order to reduce the concentrations of reaction-producing soluble antigens and ingredients carried over from the medium.

The final vaccine is tested according to the U.S. standards. In addition to tests for sterility and safety, the vaccine must be tested for nitrogen content and potency. The later is determined by a protection test in mice immunized with graded doses of vaccine and challenged with an intraperitoneal injection of a mucin suspension of a mouse virulent strain (Ty 2), compared against a U.S. standarad vaccine preparation. The vaccine under test must have a potency of at least 0.6 times the standard.

Use and Contraindications

The standard regimen for adults consists of 2 doses of 0.5 mL each subsutaneously at an interval of 3 to 4 weeks. Booster doses, when indicated, given at 3-year intervals, consist of 0.5 mL subcutaneously or 0.1 mL intradermally (acetone-killed vaccines are not recommended for intradermal injection because of the likelihood of excessive reactions). Proportionately reduced doses are recommended for children. Administration of the vaccine should be deferred in the presence of acute infections. It is generally believed that immunosuppressive agents may interfere with the effectiveness of the

vaccine, although this is not well defined. Persons who have exhibited marked reactions to previous injections should be given reduced doses for booster injections.

Safety

Inoculation with typhoid vaccine is frequently followed by local tenderness and swelling at the injection site, often accompanied by mild to moderate fever generally lasting overnight but rarely more than 24 hours. Such reactions appear to be due, in primary immunization, to endotoxins, but there is clearcut evidence that untoward reactions—probably of the Arthus or delayed-sensitivity types—are especially common among individuals who have had repeated inoculations of typhoid vaccine. For this reason, booster injections should be given in smaller doses (0.1 mL) intradermally. In general, this procedure does appear to reduce the incidence and severity of untoward reactions; however, it has been found that acetone-killed and dried vaccines, for as yet unexplained reasons, cause a high incidence of severe local reactions with intradermal injections and hence this route is contraindicated with such vaccines.

Major reactions with permanent sequlae or death following typhoid vaccination are virtually unknown, and it is clear that there is no evidence that bacterial endotoxins in the quantities present in bacterial vaccines can cause permanent sequlae. Moreover, the risk of excessive reactions is reduced by the mandatory ceiling on the nitrogen content of the vaccine. The vaccine must conform to the Bureau of Biologics' requirements for safety testing in animals.

Efficacy

Until fairly recently, typhoid vaccines were prepared and used on a purely empirical basis. However, in recent years at least 10 well-controlled field trials have been carried out with various types of typhoid vaccine, in 5 different countries. It has been found that the efficacy of a particular vaccine varies considerably with the method of killing and the preservative added. Thus acetone-dried or formalin-killed whole cell vaccines have given up to 90 percent protection against "ordinary" exposure; heat-killed, phenol-preserved vaccines gave somewhat less, or, if freeze-dried, considerably less protection. Alcohol-killed and preserved vaccines have given mediocre (30 to 50 percent) protection and chemical extracts and a vaccine prepared without H antigen have given little or no protection. (None of these last three classes of vaccine is in use within the United States.) It should be noted that studies in human volunteers indicate that against very large infectious doses of typhoid bacilli, even the best vaccines are ineffective.

As regards laboratory tests, the mouse protection test required by the Bureau of Biologics correlates with the field results in the case of acetone-killed and dried vaccines and also with freeze-dried heat-killed phenol-preserved vaccines. However, the mouse protection test correlates poorly with the results in man with alcohol-type vaccines. No such comparisons have been made with thimerosal-preserved vaccines.

The excellent field results with acetone-killed and dried vaccines were obtained with vaccines reconstituted just before use. However, the efficacy of such vaccines when distributed in the liquid state cannot be assumed to be identical.

Introduction of thimerosal as a preservative has not been tested by field trials. Nevertheless, laboratory tests show that thimerosal preservation is generally less deleterious than phenol and heat. The essentials concerning the various existing vaccines are shown in Table I.

It should be noted that no field trials have been carried out with typhoid vaccine prepared by any U.S. manufacturer. Nevertheless, the available typhoid vaccines are produced by methods similar to those employed for the production of vaccines that proved effective in field trials, or have introduced changes that could not, *a priori*, be considered necessarily deleterious to the efficacy of the product. In spite of the uncertainties introduced by differing techniques of inactivation and preservation, the Panel considers that there is reasonable evidence of efficacy of available typhoid vaccines.

Special Problems

The major problem associated with typhoid vaccine is the lack of a laboratory test of potency that correlates consistently with field results with various vaccines in man. Furthermore, changes in preparation of the vaccine, even those that may be expected to be beneficial, create uncertainty in its evaluation. Meanwhile, however, it would be useful to study further the correlation of laboratory tests with human trials of formalin-preserved vaccine (see Table I).

This problem however, can only be treated empirically until the mechanisms of immunity to typhoid fever are defined. Present knowledge indicates that immunity is not dependent on either H or Vi antigens alone, but that H antigen may be an essential component; however, it is possible that another, perhaps unidentified, antigen is also essential. It is not clear whether immunity is primarily humoral or cellular, systemic or local. If and when these questions are answered it should then be possible—in collaboration with studies in the field or in human volunteers—to identify a laboratory test that correlates satisfactorily with human protection. Related to the above is the problem of preparing a less reactive vaccine.

TABLE I.—INFORMATION ON CHARACTERISTICS OF CURRENT TYPHOID VACCINES

Type	Effectiveness in field trials	Mouse protective potency	Antibody response in man			Stability	Reactions
			H	O	Vi		
Heat-killed, formalin preserved.	+++	++	+	+	+	?	?
Acetone-killed, kept in dry state.	++ to +++	++	+	+	++	+++	+++ (intradermal) + (s.c. or i.m.)
Heat-killed, phenol preserved.	+ to ++	+	++	+	±	++	+ (any route)
Alcohol-killed and preserved.	±	++	+	+	++	++	++
Thimerosal killed and preserved.	?	++	+	+	+	++	+
Acetone-killed, thimerosal preserved.	?	++	+	+	+	Variable	+

± = borderline.
? = unknown.
+, ++, +++ = relative scale of response.*
*Because of variation in field and laboratory procedures only a relative scale is used in the table.

Recommendations

1. Appropriate support should be given to studies aimed at clarifying the immune mechanism(s) in typhoid fever.

2. Field or volunteer studies designed to test promising vaccines or their fractions for protection against typhoid fever should be supported.

3. The search for laboratory tests that correlate well with results of vaccination in man should be continued.

Basis of Classification

Proof of efficacy of typhoid vaccine is tied almost exclusively to field trials that are not feasible except in high endemic areas of the world. Classification of efficacy is therefore based upon production and preservation of vaccines known to be successful in such trials and supported by a mouse protection test correlated with field results. Methods of inactivation and preservation of those vaccines that have not been previously subjected to field trials have been accepted by the Panel because on theoretical grounds there is no basis to believe that they would interfere with efficacy.

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SPECIFIC PRODUCT REVIEWS

Typhoid Vaccine Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* The vaccine is made from heat-killed *Salmonella typhi* (Ty 2 strain), suspended in phosphate buffered saline to a concentration of not more than $1,000 \times 10^6$ cells per mL. The material prepared since 1969 is preserved with 0.01 percent thimerosal. The vaccine contains 8 protective units per mL.

2. *Labeling*—a. *Recommended use/indications.* The labeling follows the Public Health Service Advisory Committee on Immunization Practices recommendations and is indicated for intimate contacts with known cases of typhoid fever or carriers; for medical or hospital personnel; and for individuals contemplating travel to endemic areas.

b. *Contraindications.* (1) Acute respiratory disease; (2) in children with histories of febrile convulsions or cerebral damage; and (3) patients on corticosteroid and/or immunosuppressive drugs—since the immune response may be suppressed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No field trials have been performed with this product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The manufacturer reports that no complaints have been received in the 10-year period from 1961 to 1972 during which many hundred thousand doses were distributed. Local reactions occurred with intradermal injections in all (27/27 adults) with a past history of typhoid vaccine (2.43 cm to 6.5×7 cm erythema).

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined with certainty because there is no supporting field trial evidence of efficacy for this specific product. However, it is likely that the benefit-to-risk assessment of this product is satisfactory. (See Generic Statement.)

4. *Critique.* Although this vaccine should meet required standards of preparation (it is heat-killed and was phenol preserved), since 1969 it has been preserved with thimerosal. The latter is presumed to be at least as desirable a method of preservation as is phenol. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Eli Lilly and Company

1. *Description.* This typhoid vaccine is a suspension of the Ty 2 strain of *Salmonella typhi* grown in a semisynthetic liquid medium. The organisms are killed by acetone which is then removed. The organisms are resuspended in buffered physiological saline, containing 0.01 percent thimerosal as preservative. The final vaccine contains no more than 1 thousand million typhoid organisms per mL, no more than 0.023 mg of nitrogen per mL. The final product is standardized to 8 protective units per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against typhoid fever under the following circumstances: (1) Intimate exposure to a known carrier; (2) community or institutional outbreaks; and (3) foreign travel to endemic areas. The label cautions against intradermal administration.

These recommendations agree fully with those of the Public Health Service Advisory Committee on Immunization Practices, as does the recommended schedule for dosage and administration.

b. *Contraindications.* It is recommended that vaccination be avoided during an acute illness. The labeling further contains a caution about the administration of typhoid vaccine during chronic steroid therapy, implying that steroid therapy may so modify host defense mechanisms that an otherwise effective vaccine may be rendered ineffective.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In a study carried out by Eli Lilly and Company (Ref. 1) when a change to acetone inactivation of the vaccine was made, 60 adult males were randomly divided into 3 groups, 2 receiving separate lots of acetone-killed vaccine, 1 receiving Eli Lilly and Company's heat-phenol inactivated vaccine. Each received two 0.5 mL doses 4 weeks apart, and some received a third dose 4 weeks later. There were observed for 48 hours each dose. No significant differences were noted among vaccine in height of H, O, or Vi antibody titer according to vaccine used. The actual data, however, are not provided.

The general body of data supporting the efficacy of acetone-killed vaccine is cited in the manufacturer's submission

(Ref. 1), but Eli Lilly and Company's vaccine per se was not used.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the study cited above, there was no difference in local reactivity among recipients of the three vaccines, although the absolute numbers were not cited. Six of the subjects complained of constitutional reaction including chills or malaise during the 48-hour observation period, but all remained afebrile, and the complaints came equally from all three vaccine groups. There were no allergic reactions.

The manufacturer's marketing experience indicates that a few million doses of the vaccine were distributed in the 5-year period 1968 to 1972, and that 18 complaints were received of local or systemic reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined with certainty owing to the lack of supporting field trial evidence of efficacy of acetone-killed vaccines perserved in the liquid state with thimerosal. However, it is likely that the benefit-to-risk assessment of this product is satisfactory. (See Generic Statement.)

4. *Critique.* This vaccine is killed by acetone but its preservation by thimerosal introduces a variable which has not yet been tested by field trial. However, animal studies and theoretical considerations strongly suggest that this vaccine should be effective in field trials. The latter may not be feasible with this product in the foreseeable future.

The labeling should be revised to reflect more current knowledge of the effect of corticosteroid therapy on immunoglobulin synthesis, particularly with regard to the dose and duration of steroid therapy. In addition, references to the need for "separate heat-sterilized syringe and needle" are quite dated, and should be revised to reflect contemporary practice as well as contemporary knowledge of hepatitis B.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* The final vaccine contains no more than 1 thousand million bacterial cells per mL (strain Ty 2) suspended in phosphate buffered saline containing 0.01 percent thimerosal. The bacilli are killed by thimerosal at room temperature, but no further details of the manufacturing process are given.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for persons for whom immunization against typhoid fever is indicated. The indications are not specified, but reference is made to the Public Health Service Advisory Committee on Immunization Practices recommendations. For primary immunization two doses of 0.5 mL subcutaneously on two occasions, separated by 4 or more weeks, are given to adults and children over 10 years of age. For children 6 months to 10 years the procedure is the same except that the dose is 0.25 mL.

Under conditions of continued or repeated exposure a single booster dose should be given at least every 3 years.

Boosters can also be given with an intradermal dose of 0.1 mL, which generally would give less reaction.

b. *Contraindications.* None are mentioned, although a warning is given to review the history of the patient regarding possible sensitivity to the product.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements and exceeds the potency of an analagous heat-killed, phenol-preserved vaccine in the mouse protection test.

(2) *Human.* No information was provided on this particular product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled, partially controlled, or uncontrolled studies have been carried out by the Massachusetts Public Health Biologic Laboratories. No fatal reaction following administration of typhoid vaccine has been documented by the Massachusetts Public Health Biologic Laboratories. However, it is well known that there many be may local reactions and some general reactions in adults following administration of the vaccine. No data from the complaint file are given.

c. *Benefit/risk ratio.* Assuming the product is effective, and the person to be vaccinated is at some risk of acquiring typhoid fever, the benefit-to-risk assessment should be satisfactory. (See Generic Statement.)

4. *Critique.* No clinical tests have been carried out on this particular product, but data from unpublished mouse protection tests suggest that the manufacturing process yields a vaccine equal or superior to vaccines of proven efficacy (see Generic Statement). The label is vague on indications for use.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The brief submission by Merck Sharp & Dohme represents a phenol-inactivated typhoid vaccine. The appropriate strain of typhoid bacilli is used and the final concentration is 1 billion organisms per mL. It is diluted in a buffered solution of physiologic sodium chloride. The preservative is phenol, 0.5 percent. The bacteria are inactivated by phenol, apparently without heat. No other information is given regarding its production.

2. *Labeling*—a. *Recommended use/indications.* The package insert, now 11 years old, recommends a dosage schedule at variance with current recommendations. The description of the method of preparation is outdated.

b. *Contraindications.* The labeling statement is acceptable.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product met Federal requirements when it was produced. No other information is supplied.

(2) *Human.* The only information provided is related to studies of generic typhoid vaccines.

b. *Safety*—(1) *Animal.* The manufacturer's submission states that the product meets Federal requirements.

(2) *Human.* No data are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* This is a typhoid vaccine, apparently phenol inactivated, which appears to meet U.S. standards for animal safety. No other information regarding its efficacy or safety is provided. The labeling is outdated.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Typhoid Vaccine Manufactured by Texas Department of Health Resources

1. *Description.* This product contains approximately 1 thousand million organisms of *Salmonella typhi* per mL, strain Ty 2, killed by heat and phenol. Diluent is 0.02 M phosphate bufered saline, pH 7.2 to 7.3; 1:10,000 thimerosal is added. Each milliliter of vaccine